LIGHT-ADJUSTABLE LENS: DEVELOPMENT OF *IN VITRO* NOMOGRAMS

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ABSTRACT

Purpose: To determine whether digital spatial intensity patterns can be developed to effect precise in vitro correction of myopic, hyperopic, and astigmatic refractive errors in a silicone light-adjustable lens (LAL). Also, to determine whether a new spatial intensity pattern for "lock-in" is effective in vitro.

Methods: A digital interferometer/irradiation system was developed to irradiate LALs and measure the power change following irradiation. Light-adjustable lenses were mounted into a wet cell maintained at 35.0 ± 0.5°C (simulated ocular temperature) and allowed to equilibrate for a minimum of 2 hours. Ultraviolet light was then applied with spatial light intensity patterns to correct hyperopia, myopia, and astigmatism. Light-adjustable lenses were also treated to effect lock-in with a separate spatial light intensity pattern. Treated lenses were characterized for power change and optical quality. In the case of lock-in, exhaustive chemical extraction was also performed to determine the percentage of remaining macromer.

Results: Appropriate digital irradiation spatial intensity patterns were created to develop nomograms for in vitro correction of myopia, hyperopia, and astigmatism in approximate 0.25 D steps. Power changes were reproducible and did not alter optical quality of the LALs. Further, lock-in dosing of the LALs did not alter optical quality or significantly change LAL power.

Conclusions: In vitro nomograms have been developed for a silicone LAL that permit precise correction of myopia, hyperopia, and astigmatism. Furthermore, a spatial light intensity pattern has been devised that effects lock-in without significantly altering LAL power or optical quality.

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INTRODUCTION

With current intraocular lens (IOL) designs and biometry, more than 95% of cataract surgery patients achieve best-corrected visual acuity of 20/40 or better.[1-3] Residual postoperative refractive error in these patients often creates a gap between uncorrected visual acuity and best-corrected visual acuity, leaving approximately one third of patients in need of spectacles for optimized distance vision. The discrepancy between postoperative corrected and uncorrected distance vision is often due to inaccurate IOL power determination and preexisting astigmatism.[4-12] Further difficulties in appropriate IOL power determination are encountered in patients who have undergone previous corneal refractive procedures.[13-16] A means to postoperatively correct residual spherical and astigmatic refractive errors after cataract surgery would allow a greater number of IOL patients to achieve the desired refractive outcome.

Previous investigators have recognized the need for an IOL with the capacity of postoperative power adjustment.[17-22] While potentially enabling adjustment of IOL power postoperatively, these lens designs require invasive adjustment procedures and/or do not allow correction of astigmatism and higher-order optical aberrations.

Recently, we reported on a silicone light-adjustable lens (LAL) that is adjusted using safe levels of ultraviolet light.[23] The LAL formulation consists of four basic components: a silicone matrix polymer, macromer, photoinitiator, and ultraviolet light absorber. The LAL material is a clear and flexible elastomer capable of

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folding during implantation. After implantation, the lens power may be increased or decreased noninvasively by the application of the appropriate spatially resolved irradiation profile. Upon irradiation with 365-nm light, the macromer molecules in the irradiated region are photopolymerized to form an interpenetrating network. This produces a concentration gradient between the irradiated and unirradiated regions of the lens. Macromers from the unirradiated portion of the lens diffuse along this concentration gradient into the photopolymerized portion of the lens to reestablish thermodynamic equilibrium. Macromer diffusion produces a swelling in the irradiated region that effects a change in the lens curvature with a concomitant power change. When the central portion of the lens is irradiated preferentially and the periphery left nonirradiated, macromer diffuses into the center of the lens, causing an increase in the lens power and a hyperopic shift (Figure 1). By irradiating preferentially the peripheral portion of the lens, macromer migrates outward, causing a decrease in lens power, producing a myopic correction. The refractive index of the macromer is designed to match the silicone matrix for optimal optical compatibility; therefore, the power change of the LAL upon irradiation is induced primarily by the shape (radius of curvature) change.

Once the appropriate power adjustment is achieved, approximately 12 to 18 hours after irradiation, the entire lens is irradiated to "lock in" and stabilize lens power by polymerizing the remaining reactive macromer. By irradiating the entire lens with the appropriate profile, there is no macromer diffusion and thus no further change in lens power.

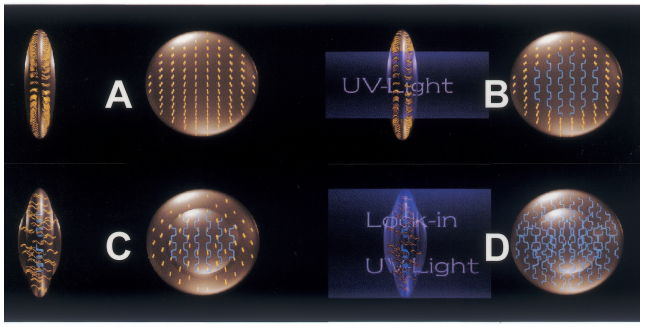


FIGURE 1
Correction of hyperopia with the light-adjustable lens (LAL). The clear material represents the matrix of the lens. Yellow strands represent macromer. The initial implant is viewed from the side and from the front (A). The central zone of the lens is treated with UV light (365 nm) to activate the photoinitiator, causing the macromer in the central zone to polymerize (blue strands) (B). At this point the shape of the lens has not significantly changed. Free macromer from the unirradiated portion of the lens diffuses down the concentration gradient between highly concentrated macromer in the unirradiated zone and depleted macromer in the irradiated zone, causing the central zone to swell (C). The increased curvature of the central zone decreases the focal length, correcting for hyperopia. Once the desired adjustment of the lens has been achieved, the adjusted lens is "locked" by irradiating the entire lens, causing all of the free macromer to polymerize without further altering the shape of the lens (D).

In our previous report, we addressed issues of biocompatibility and efficacy of the LAL in a rabbit model.[23] Preliminary efforts at developing a nomogram for myopic adjustments of LAL power were also presented. Herein we determine whether digital spatial intensity patterns can be developed to effect precise in vitro correction of myopic, hyperopic, and astigmatic refractive errors. We also test a new spatial intensity pattern for lock-in.

METHODS

Work was performed at Calhoun Vision, Inc, Pasadena, California. A digital interferometer/irradiation system was developed in the laboratory to irradiate the LALs and measure the power change following irradiation. There are two main components of this optical instrument (Figure 2). The first is the irradiation system, which is composed of a mercury (Hg) arc lamp filtered to 365 nm (±5 nm full width half maximum), a critical illumination/projection system, and a digital mirror device. This device is a pixelated, micromechanical spatial light modulator formed monolithically on a silicon substrate. Typical digital mirror device chips have dimensions of 15.1 mm × 12.7 mm. The individual micromirrors are 13 to 17 µm on an edge and are covered with an aluminum coating. The micromirrors are arranged in an *xy* array, and the chips contain row drivers, column drivers, and timing circuitry. The addressing circuitry under each mirrored pixel is a memory cell that drives two electrodes under the mirror with complementary voltages. Depending on the state of the memory cell (a "1" or "0"), each mirror is electrostatically attracted by a combination of the bias and address voltages to one of the other address electrodes. Physically the mirror can rotate ±10 degrees. A "1" in the memory causes the mirror to rotate +10 degrees, whereas a "0" in the memory causes the mirror to rotate –10 degrees. A mirror rotated to +10 degrees reflects incoming light into the projection lens and onto the LAL. When the mirror is rotated –10 degrees, the reflected light misses the projection lens and

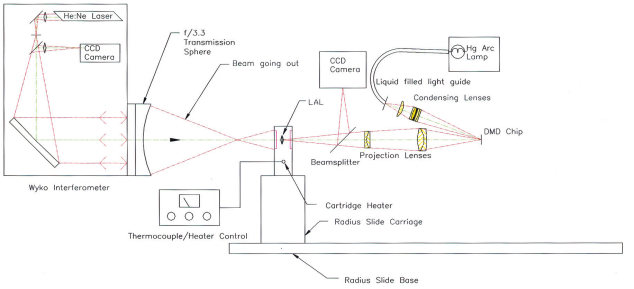


FIGURE 2
Optical schematic of the interferometer/irradiation system.

LAL. Thus, the great utility and advantage of the digital mirror device in its relation to the LAL is the ability to easily define a particular spatial intensity profile, program this into the device, and then irradiate the LAL. Because of the digital nature, the digital mirror device technology offers greater resolution of the spatial light profile, enabling the delivery of more precise, complex patterns to provide greater range and control to the LAL corrections.

The optical analysis portion of this instrument utilizes a phase-shifting Fizeau interferometer (Wyko model 400) operating in double-pass configuration fitted with a 4-inch transmission sphere. In practice, a set of LALs is first mounted into the wet cell maintained at 35.0 ± 0.5°C (simulated ocular temperature) and allowed to equilibrate for a minimum of 2 hours. The wet cell is adjusted along the optical axis of the interferometer until the power in the wavefront across the full test aperture is minimized (≤ 0.010 waves). A measurement of the wavefront in the exit pupil of the LAL and its position along the radius slide are recorded, followed by irradiation of the lens. The total time for macromer diffusion is between 12 and 18 hours and depends upon the applied intensity and time. At 24 hours after irradiation, the LALs are returned to their original position on the radius slide followed by measurement of the LAL's adjusted wavefront. Analysis of the postirradiated wavefront, along with subtraction of the preirradiated and postirradiated wavefronts, gives direct information regarding the magnitude of the induced power change, the size of the affected area, and any changes in the other aberrations induced by the irradiation procedure (eg, spherical aberration, coma, astigmatism). Knowledge of the spatial intensity profile applied to the LAL, coupled with the analysis of the altered wavefront, allows guidance in the modification of the pattern to produce the desired changes.

The LALs before and after irradiation were characterized for power change and optical properties by measuring magnification (line pair separation method), resolution (US Air Force target method), and modulation transfer function.[24] The spectral transmittance of the preirradiated and postirradiated LAL material was also assessed by ultraviolet-visible spectrophotometry.

To assess lock-in efficacy, exhaustive chemical analysis of extractables was used to determine the percentage of remaining macromer.

RESULTS

Figure 3 shows spatial intensity patterns for correction of hyperopia (a) and myopia (b) and a "flat-top" spatial intensity pattern used for lock-in irradiation (c).

A representative 2 D myopic adjustment is shown in Figure 4a, where the periphery of the LAL was irradiated,

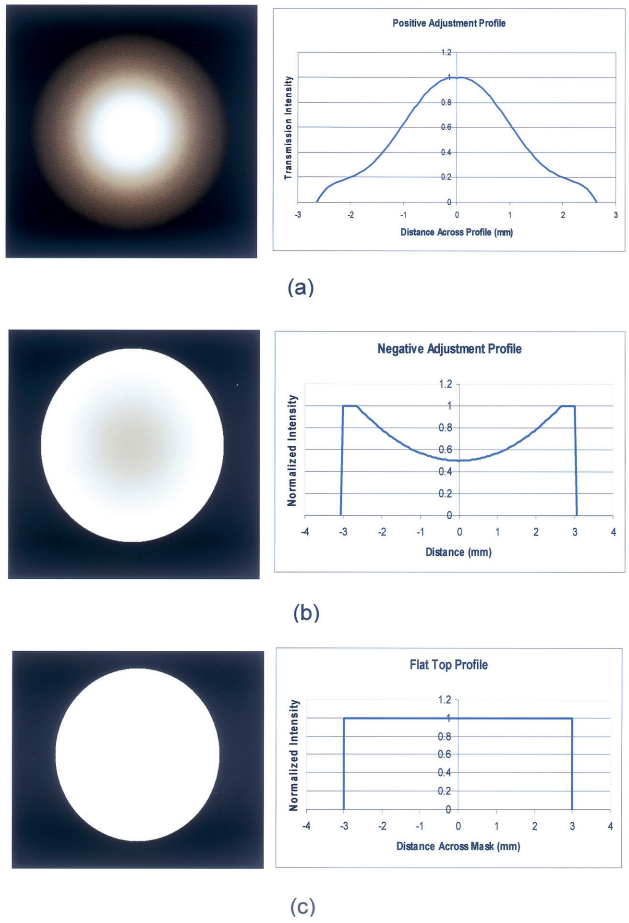


FIGURE 3
Digital (left column) and graphic (right column) representations of spatial intensity profiles for (a) hyperopic adjustment, (b) myopic adjustment, and (c) lock-in treatment ("flat top" profile).

causing the diffusion of macromers from the central portion of the lens out to the lens periphery. The interference fringes are depicted 24 hours after irradiation at the preirradiation focus position. The most striking feature of this figure is the addition of approximately 12 fringes (in double pass) of defocus (optical path difference) added to the lens, which corresponds to –2.0 D of myopic correction.

Optical characterization of the LALs before and after irradiation by measuring resolution (US Air Force target method), modulation transfer function,[24] and spectral transmittance shows no significant change following irradiation (Figure 4b, c, d).

Results from optical testing to generate nomograms for myopia and hyperopia are shown in Figure 5. Dose-response curves are generated with gradations of approximately 0.25 D from +0.75 D to +2.50 D for hyperopia and –0.5 D to –2.75 D for myopia. Adjustments are obtained with a precision of ≤ 0.25 D.

The flat-top lock-in spatial intensity patterns achieved

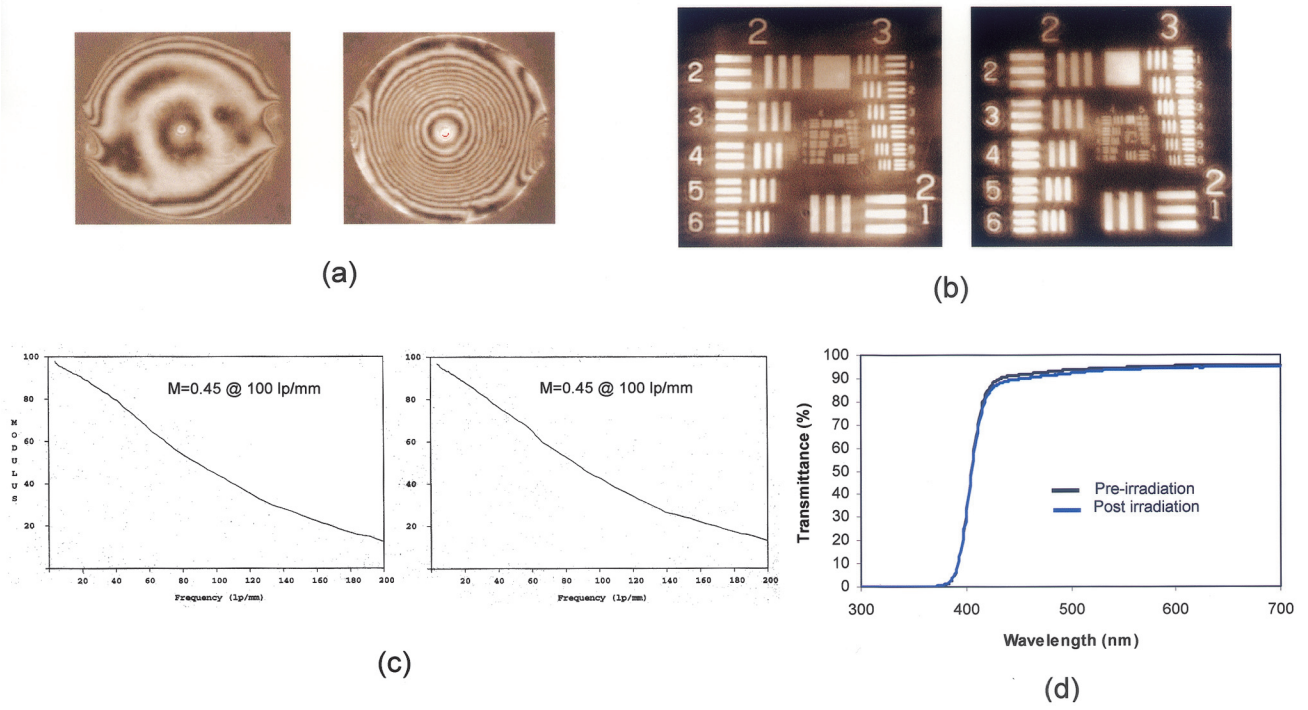
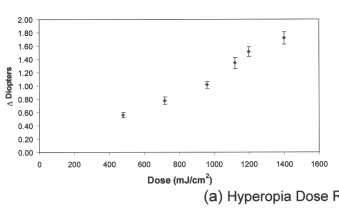


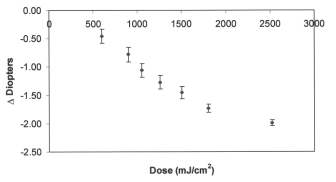
FIGURE 4

Optical testing of the light-adjustable lens (LAL) upon irradiation. (a) Fizeau interference fringes of an LAL (base power +20 D) immersed in water at 35ºC before irradiation at best focus (double pass) and 24 hours after irradiation showing the addition of about 12 fringes (-2 D) to the preirradiated lens, (b) resolution efficiency of an LAL before and after irradiation through a standard 1951 USAF target, (c) modulation transfer function curve before and after irradiation, and (d) light transmittance curve before and after irradiation.



Dose (mJ/cm^2)	Average ΔD Spectacle Plane	St. Dev
480	0.56	0.04
720	0.78	0.06
960	1.01	0.05
1120	1.34	0.08
1200	1.51	0.07
1400	1.72	0.10

(a) Hyperopia Dose Response Table and Curve



Dose (mJ/cm^2)	Average ΔD Spectacle Plane	St. Dev
600	-0.46	0.12
900	-0.78	0.13
1050	-1.06	0.12
1260	-1.27	0.12
1500	-1.46	0.11
1800	-1.73	0.07
2520	-1.99	0.05

(b) Myopia Dose Response Table and Curve

FIGURE 5

Hyperopic (a) and myopic (b) nomograms demonstrating reproducible power adjustments with a precision of ±0.25 D. Each point on the nomogram consists of a minimum of 16 light-adjustable lenses per dose.

successful lock-in of the LALs. This was confirmed by exhaustive chemical extraction of explanted LALs from the in vivo study in a rabbit model, which showed less than 1% remaining macromer. Results of photolocking 48 LALs demonstrate a change in lens power of less than 0.25 D (–0.08 ± 0.19) without altering lens optical quality as determined by resolution efficiency (≥4-3) and modulation transfer function measurement (0.43 ± 0.04).

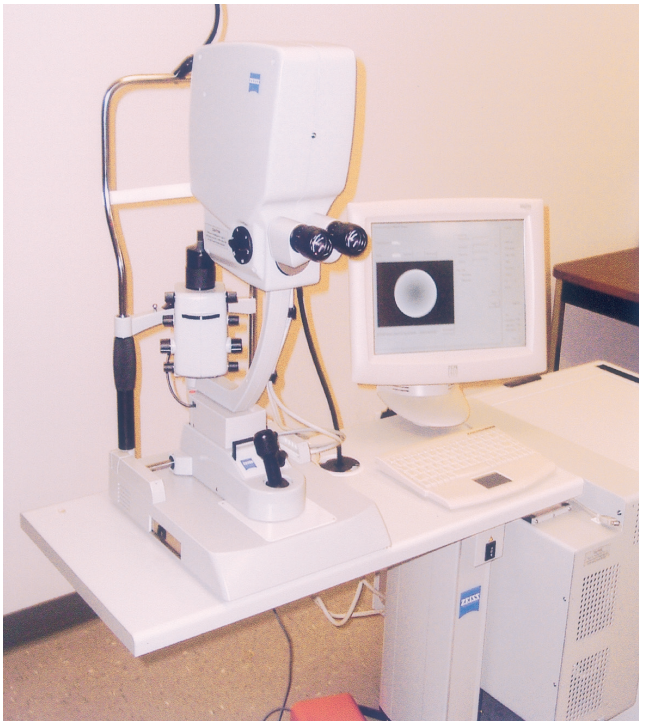
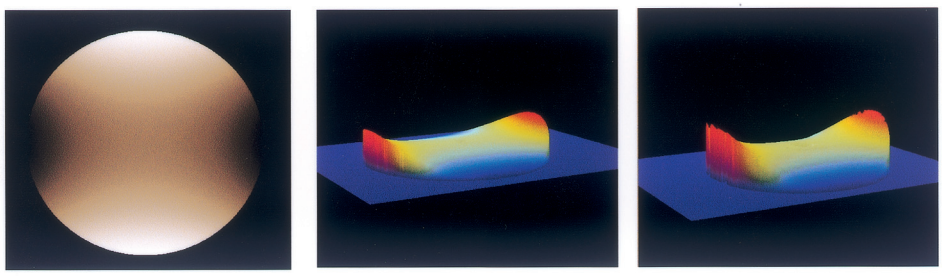


FIGURE 6

Digital light delivery device, developed in collaboration with Zeiss-Meditech.



Digital image of stigmatic correction spatial intensity profile

1.2 D between the saggital and tangential axes 0.9 J/cm² Dose

1.5 D between The saggital and tangential axes 1.1 J/cm² Dose

(a) (b)

Dose (mJ/cm^2)	Average ΔD Spectacle Plane	St. Dev
750	1.05	0.05
900	1.27	0.07
1050	1.48	0.07
1200	1.74	0.07
1680	2.11	0.16

FIGURE 7

Astigmatic correction (a) digital image of spatial intensity profile, (b) 3-D wavefront presentation of irradiated light-adjustable lenses, and dose-response table.

An astigmatic nomogram was generated using the Zeiss digital light delivery device with an embedded digital mirror device[23] (Figure 6). The digital pattern projected onto the LAL is shown in Figure 7a. Representative three-dimensional wavefronts of two irradiated LALs are shown in Figure 7b. The table in Figure 7 shows dose-response data demonstrating inducement of astigmatic power changes with approximate 0.25 D steps between 1.0 and 2.0 D.

DISCUSSION

We demonstrate that appropriate digital irradiation spatial intensity patterns could be devised to create nomograms for in vitro correction of myopia, hyperopia, and astigmatism in the LAL. Using the appropriate spatial intensity profile, nomograms with approximate 0.25 D steps were developed. Power changes were reproducible and did not alter optical quality of the LALs. Further, we demonstrate that lock-in dosing of the LALs did not alter optical quality nor significantly change LAL power. While our previously reported study of the LAL showed a good correlation between in vitro and in vivo adjustments in a rabbit model, translating the current work into nomograms for clinical use remains untested.

The human cornea has significant and important differences from the rabbit that may limit the use of nomograms presented above.[25,26] The rabbit cornea is about two thirds as thick as the human cornea and lacks Bowman's layer. Because the differences may affect light transmission as well as scattering, use of the spatial light intensity patterns and dosing may need to be altered as the LAL is used clinically.[27,28]

With respect to corneal light transmission at 365 nm in humans, there is considerable variation reported in the literature. Values have ranged from 20% to 75%.[29-31] This large discrepancy may be explained by studies measuring total (measurement of both the forward transmitted and scattered light) versus direct (light transmitted through a 1-degree cone) transmission, a much smaller value. Also, these measurements have been performed in vitro on eye bank corneas and are not necessarily predictive of what will be encountered in vivo.

Thus, although we have demonstrated the feasibility of these novel IOL materials to be adjusted precisely to correct hyperopia, myopia, and astigmatism, the practicalities of using this system in patients remains to be determined.

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DISCUSSION

Dr Roger F. Steinert. Dr Schwartz and his colleagues have described another key step in their development of a novel technology. The ability to adjust the power and possibly other optical characteristics of an IOL, such as modifying multifocality and reducing high-order aberrations, has captured the imagination of cataract and refractive surgeons worldwide. Rarely is pre-clinical technology so well known and repeatedly discussed by clinicians. From the point of view of an outside observer keenly intrigued by the potential for this device, the process of this development has been characterized by a rigorously designed and meticulously achieved series of milestones.

The current presentation is essentially a proof of concept. After conceiving the chemical principle of migrating macromolecules that could be polymerized after IOL implantation by light, and then developing the material in a form suitable for a lens, the inventors faced the challenge of precise control of the delivery of the light energy. This required the development of the digital light delivery system whose key component is the digital mirror

device (DMD).

In an *in-vitro* laboratory setting, Dr. Schwartz and his coworkers have now developed nomograms for control of both hyperopic and myopic lens power changes presented here. The standard deviations are impressively tight, well within clinically acceptable levels. Details about methodology need to be expanded, however. The text indicates that "each point on the nomogram consists of a minimum of 16 LALs/dose," implying that the number of lenses tested varied from group to group. Why? Were some results unexpected and the outliers discarded? If so, the standard deviation is artificially small. Similarly, we would like much more detail about the lenses that were photo locked and then tested for optical stability and resolution. Summary results are presented on 48 photo locked LALs, again with apparently tight variability, but the text is silent on the underlying data and method of statistical analysis as well as the possibility of discarded data points.

Beyond these technical points, however, the authors appropriately alert us to some of the future challenges. One key question is the consistency of transmission of the 365-nanometer light by corneas of different patients. Another major issue is safety. While safety concerns are beyond the scope of the current presentation, the inventors will need to demonstrate the short- and long-term safety of both the material and the ultraviolet light, whose wavelength is toxic to the retina and the corneal epithelium. I have been assured that these concerns are well known and being satisfactorily addressed by the researchers.

Other issues will arise as this technology moves into clinical testing. Some of these issues are practical, such as the need for patients to wear UV absorbing spectacles, at least outdoors, in the days or weeks prior to photo locking, and whether patients will comply with this.

Many other issues are socioeconomic. The technology of the digital light delivery system, the IOL material itself, and the considerable extra surgeon and technician time involved in the postoperative interventions all add considerable expense. As with some other new IOL technologies, such as the accommodating IOL, the restrictions on balance billing of cataract patients have forced a business model in the U.S. where these expensive technologies are marketed for refractive lens exchange in patients without lens opacities. How much extra is such a patient willing to pay for optical perfection?

Notwithstanding these challenges, known and unknown, Dr Schwartz and his coworkers are to be congratulated both for their innovative technology and for their methodical scientific development of its potential.

Dr David L. Guyton. To do the lock-in process, you have to have a very widely dilated pupil to irradiate the whole lens. There are many cataract patients whose pupils do not dilate well. How critical do you view this problem and do you have a solution for those cases where the pupil just won't dilate?

Dr Michael Nork. As a retinal specialist, I was hoping that we had seen the end of silicone lenses since these hydrophobic lenses present a difficulty when performing retinal operations. The lenses develop condensation, making it difficult to see the retina once you perform an air-fluid exchange. Although it is true that most people with implants will never require a vitrectomy procedure, on the other hand, most people that need vitrectomy surgery are pseudophakic. Is there any way to coat the lens or technologies to prevent condensation from forming during air-fluid exchanges?

Dr George L. Spaeth. From the point of view of quality of life, what would be the benefit to the patient? Resources are limited. Is the investment in this type of technology justified in terms of other issues that need to be solved?

Dr Daniel M. Schwartz. First, I would like to address the issue of the number of lenses used for adjustment nomograms and lock-in. As Dr Steinert notes, there were variable numbers of lenses used to develop each point of the nomograms. Our in-vitro lens adjustments/lock-ins are performed in groups of eight lenses by one to three scientists. The nomogram data reported ranged from 16 to 48 lenses for each point generated by a minimum of two different operators and represents the total number of lenses tested under each condition. All data collected were reported with no data points rejected. In spite of the different operators, the data remained reproducible with small standard deviations.

Dr Steinert also raises the important potential problem of variable corneal transmission of 365-nanometer light used to irradiate the lenses. This is an important issue because if there is variability from patient to patient, it's going to make this technology very difficult to adopt by the practitioner. With the data to date, we don't know how much variability there's going to be from patient to patient. However, we have adjusted eight consecutive patients since the manuscript was submitted. Four were adjusted with an intended refractive change of +1.5 diopters, 2 for +1.0 diopters, and 2 for -1.0 diopters. After adjustment, all were within 0.25 diopters of the intended refractive outcome. One of the patients we adjusted for +1.5 diopters was 50 years old and one was 85, and yet we achieved the same dioptric change. We are using pachymetry measurements before and after surgery to confirm that patients recover to their pre-op

pachymetry levels, thus minimizing corneal edema as a variable. Fortunately, the technology is somewhat tolerant of these differences. We can get the same power changes with about a 10 percent difference in corneal light transmission.

There are concerns about irradiation safety, and these relate to potential damage to the cornea with photokeratitis or damage to the retina from these UV light sources. There is animal and human data on these potential toxicities. The threshold for toxicity for photokeratitis is approximately 70 joules per cm^2 at 365 nm. We have not encountered any cases of photokeratitis either in our rabbit studies for preclinical submission to the FDA or in the patients that we have treated.

We also are concerned about retinal toxicity, and the retinal threshold in primates at this wavelength is approximately 5.5 joules per cm^2. Dr David Sliney is widely published on the subject of the effects of UV radiation on the eye and serves as member, advisor and chairman of numerous committees and institutions which are active in the establishment of safety standards for protection against non-ionizing radiation (ANSI, ISO, ICNIRP, ACGIH, IEC, WHO, NCRP). He has advised that we not exceed 2 joules per cm^2 at the retina, and light treatments are within that guideline.

Dr Steinert raised some important issues about the expense of the technology and the time requirement for practitioners. I do not have detailed information about these issues, but I can say the lens material itself is surprisingly inexpensive. It costs just a few dollars more to make this lens than conventional silicone lenses. The sales price for the digital light delivery device is approximately $80,000, which compares favorably with the excimer laser.

As Dr Guyton notes, pupillary dilation is very important. For typical adjustment and lock-in, spatial intensity profiles are projected onto nearly the entire 6mm diameter of the IOL. We can customize the size of the adjustment profile to accommodate smaller pupils; however, the entire lens must be irradiated for lock-in. At this time we are limiting the technology to patients who dilate 7mm or more preoperatively. Undoubtedly there will be some patients who dilate less after surgery. For those patients, we could use a gonioscopic-type lens that would direct light around the edges of the pupil to achieve lock-in. We are also developing a second-generation lens formulation that will not require lock-in. Pupillary dilation would not be an issue with such a formulation since lock-in would not be necessary.

Dr Nork raises an important issue about condensations that can form on silicone IOLs during vitrectomy surgery, especially when silicone oil is used. The development of proliferative vitreoretinopathy (PVR) requiring vitrectomy among those patients who develop pseudophakic retinal detachments is probably on the order of 5 to 7 percent. With PVR, equal success is achieved using either gas or silicone oil, so silicone oil would be avoided in patients with a silicone light adjustable lens. For those patients in whom there is an increased risk of retinal detachment recognized prior to the cataract surgery, an adjustable silicone lens may not be indicated. We are not restricted to silicone lenses and we can adapt our technology to acrylic lenses, thereby avoiding these condensation issues. We have developed a prototype acrylic formulation that has been successfully adjusted.

Dr Spaeth asks how is this going to make our patients' lives better, and is it really worth the cost? I do believe that there is a need for this technology since more patients would like to be spectacle-free both at near and distance. I have discussed a monofocal version of this lens, but we can also make a customized multi-focal version of the lens. Using the digital light delivery device, we can emmetropize the eye and then create a multi-focal optic *in situ*. Furthermore, if a patient will not tolerate multi-focality, the multi-focal optic is potentially reversible. Because of the ability to modify lens power multiple times until it is locked in, we can also try a patient with monovision and then reverse it if the patient wishes. As discussed above, the technology is going to be a fairly insignificant increase in cost in terms of the IOL material. Whether patients themselves will want to undergo implantation with an adjustable IOL given the extra cost related to financing the light delivery device and physician time, only the market will provide the answer. You still have to perform a refraction, but the physician time for adjustment and lock-in is minimal. Treatments are on the order of 30 seconds to two minutes each for adjustment and lock-in.